Complete Summary

GUIDELINE TITLE

Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society.

BIBLIOGRAPHIC SOURCE(S)

Utian WH, Archer DF, Bachmann GA, Gallagher C, Grodstein F, Heiman JR, Henderson VW, Hodis HN, Karas RH, Lobo RA, Manson JE, Reid RL, Schmidt PJ, Stuenkel CA. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. Menopause 2008 Jul-Aug;15(4 Pt 1):584-602. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: The North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause* 2007 Jan 31;14(2):168-82. [145 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Menopause-associated symptoms in perimenopausal and postmenopausal women

GUIDELINE CATEGORY

Counseling
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Geriatrics
Internal Medicine
Obstetrics and Gynecology
Oncology

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To update for both clinicians and the lay public the evidence-based position statement published by The North American Menopause Society (NAMS) in March 2007 regarding its recommendations for menopausal hormone therapy (HT) for postmenopausal women, with consideration for the therapeutic benefit-risk ratio at various times through menopause and beyond
- To clarify the benefit-risk ratio of HT—as either estrogen therapy (ET) or combined estrogen-progestogen therapy (EPT)—for both treatment of menopause-related symptoms and disease prevention at various times through menopause and beyond

TARGET POPULATION

Perimenopausal and postmenopausal women

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Risk Assessment

1. Pretreatment evaluation including comprehensive history and physical examination, with mammography as applicable
2. Bone densitometry, on a case-by-case basis
3. Consideration of individualized benefit-risk ratio for hormone therapy (HT)

Management/Treatment

Individualized hormone therapy, including

1. Estrogen therapy (ET): local and systemic
2. Combined estrogen-progestogen therapy (EPT)
3. Progestogen therapy: progesterone, progestin

Note: This position statement focuses on the use of HT products available by prescription in the United States and Canada. It does not include other hormones, such as estrogen agonists/antagonists (formerly called selective estrogen-receptor modulators), those available without a prescription (including phytoestrogens), and testosterone therapy.

MAJOR OUTCOMES CONSIDERED

The risk-benefit ratio of peri- and postmenopausal estrogen therapy (ET) and estrogen-progestogen therapy (EPT) for both disease prevention and treatment of menopause-related symptoms

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A comprehensive literature search was conducted using the database MEDLINE with appropriate search words—including menopause, perimenopause, postmenopause, estrogen, progestogen, hormone therapy, hormone replacement therapy, vasomotor symptoms, vaginal atrophy, sexual function, urinary health, quality of life, osteoporosis, coronary heart disease, venous thromboembolism, stroke, total mortality, diabetes mellitus, endometrial cancer, breast cancer, mood, depression, dementia, cognitive decline, premature menopause, premature ovarian failure, natural hormones, bioidentical hormones, and Women`s Health Initiative—to identify all new papers published subsequent to the 2007 position statement. Some relevant papers were also provided by the panelists.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

An Advisory Panel of clinicians and researchers expert in the field of women's health was enlisted to review the March 2007 North American Menopause Society (NAMS) position statement, evaluate literature published subsequent to the previous position statement of 2007, conduct an evidence-based analysis, and attempt to reach consensus on recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The position statement was reviewed and approved by The North American Menopause Society (NAMS) 2007-2008 Board of Trustees as an official NAMS position statement.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The North American Menopause Society (NAMS) strongly recommends use of uniform and consistent terminology when describing hormone therapy (HT):

- ET: Estrogen therapy
- EPT: Combined estrogen-progestogen therapy
- HT: Hormone therapy (encompassing both ET and EPT)
- Progestogen: Encompassing both progesterone and progestin
- Systemic therapy: HT administration that results in absorption in the blood high enough to provide clinically significant effects; in this paper, the terms ET, EPT, HT, and progestogen are presented as systemic therapy unless stated otherwise stated
- Local therapy: Vaginal ET administration that does not result in clinically significant systemic absorption
- Timing of HT initiation: The length of time after menopause when HT is initiated

Definitions for additional potentially confusing terminology used in this guideline are found below:

- Spontaneous/natural menopause: The final menstrual period (FMP), confirmed after 12 consecutive months of amenorrhea with no obvious pathologic cause
- Induced menopause: Permanent cessation of menstruation after bilateral oophorectomy (i.e., surgical menopause) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or pelvic radiation therapy)
- Perimenopause/menopause transition: Span of time when menstrual cycle and endocrine changes occur a few years before and 12 months after the final menstrual period (FMP) resulting from natural menopause
- Premature menopause: Menopause reached at or under age 40, whether natural or induced
- Early menopause: Natural or induced menopause that occurs well before the average age of natural menopause (51 years), at or under age 45
- Premature ovarian failure: Ovarian insufficiency experienced under age 40, leading to permanent or transient amenorrhea
- Early postmenopause: The time period within 5 years after the FMP resulting from natural or induced menopause

Understanding Risk

Confusion can arise among healthcare providers, the lay public, and the media when general concepts of risk are discussed. Understanding HT risks in particular is critical to clinical decision making around menopause and beyond. Since these issues are crucial to a discussion of the role of HT in an individual woman, this position statement addresses risk concepts in a special addendum to this paper (see Addendum A in the original guideline document).

Benefits and Risks of HT

Use of HT should be consistent with treatment goals, benefits, and risks for the individual woman. The benefit-risk ratio for an individual woman continually changes with her age and her menopause-related symptoms (e.g., vasomotor symptoms, sleep disturbance, vaginal atrophy, dyspareunia, or diminished libido), any of which may have an adverse impact on quality of life (QOL). Risk factors are related to a woman's baseline disease risks; her age; age at menopause; cause of menopause; time since menopause; prior use of any hormone; types, routes of

administration, and doses of HT used; and emerging medical conditions during treatment.

Vasomotor Symptoms

ET, with or without the use of a progestogen, is the most effective treatment for menopause-related vasomotor symptoms (i.e., hot flashes and night sweats) and their potential consequences (e.g., diminished sleep quality, irritability, and reduced QOL). Treatment of moderate to severe vasomotor symptoms remains the primary indication for HT. Every systemic ET and EPT product has regulatory agency approval for this indication.

Vaginal Symptoms

ET is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy (e.g., vaginal dryness, dyspareunia, and atrophic vaginitis). Many systemic ET and EPT products and all local vaginal ET products have regulatory agency approval for treating these vaginal symptoms. When HT is considered solely for this indication, local vaginal ET is generally recommended.

Sexual Function

Relief of moderate to severe vaginal atrophy with systemic ET/EPT or local ET can be effective in relieving dyspareunia, a common cause of intercourse avoidance. One oral systemic ET product is approved in the United States for the treatment of pain with intercourse. HT is not recommended as the sole treatment of other problems of sexual function, including diminished libido.

Urinary Health

Local ET may benefit some women with urge incontinence who have vaginal atrophy. Whether ET by any route is effective in treating overactive bladder is unclear. There is controversy as to whether local ET can improve certain cases of pure stress incontinence. On the other hand, systemic HT may worsen or provoke stress incontinence, perhaps related to changes in uterine volume or periurethral collagen.

The use of local ET may help reduce the risk of recurrent urinary tract infection (UTI) by a direct proliferative effect on the urethra and bladder epithelia helping to restore the acidic environment and normal lactobacillus-predominant flora of the vagina, thus discouraging colonization of the vagina by pathogens associated with UTI. Clinically, only ET administered by the vaginal route has been shown in a randomized controlled trial (RCT) to be effective in reducing the risk of recurrent UTI. However, no ET/EPT product has regulatory agency approval for any urinary health indication.

Change in Body Weight/Mass

In women, the hormonal changes associated with the menopause transition can affect body composition and add to the tendency to gain weight. No statistically

significant difference in mean weight gain or body mass index (BMI) has been demonstrated between women who use HT and those who do not.

Quality of Life

Although no HT product has regulatory agency approval for enhancing QOL, an improvement in health-related quality of life (HQOL) can result with HT use because of decreased menopause symptoms and perhaps other mechanisms, including a possible elevation of mood that leads to a feeling of well-being. Whether HT improves HQOL in asymptomatic women is unknown. Nor are data available to determine the effect of HT on global QOL, the sense of well-being whether symptoms or physical impairments are present or absent.

Osteoporosis

Extended use of HT is an option for women who have established reduction in bone mass, regardless of menopause symptoms, for prevention of further bone loss and/or reduction of osteoporotic fracture when alternate therapies are not appropriate or cause side effects, or when the benefit-risk ratio of the extended use of alternate therapies is unknown.

Cardiovascular Effects

Three primary cardiovascular effects are discussed: coronary heart disease (CHD), stroke, and venous thromboembolism (VTE).

Coronary Heart Disease

Most observational and preclinical studies support the potential benefits of systemic ET/EPT in reducing the risk of CHD. Most RCTs do not. However, it is now understood that the characteristics of women participating in observational studies are markedly different from those of women enrolled in RCTs, and that these demographic or biologic differences, or both, influence baseline cardiovascular risks and the effects of HT on cardiovascular risk.

Timing of initiation. RCTs are in general agreement with observational studies indicating that HT may reduce CHD risk when initiated in younger and more recently postmenopausal women. In a secondary analysis of Women's Health Initiative (WHI) data, results showed a statistical trend of an HT effect relative to placebo on CHD by time since menopause, indicating that women who initiate HT more than 10 years beyond menopause are at increased risk for CHD, and those women who initiate HT within 10 years of menopause tend to have a decreased risk for CHD.

Duration of therapy. Observational studies suggest that longer duration of HT use is associated with reduced risk of CHD and mortality. The WHI RCTs and the WHI observational study suggest a pattern of lower risk of CHD among women who used HT for 5 or more years, but this is not conclusive.

In contrast, in the short term, HT may possibly be associated with an increase in CHD risk among women who are more distant from menopause at the time of HT initiation.

Coronary artery calcium. Observational studies show that long-term use of HT is associated with less accumulation of coronary artery calcium, which is strongly correlated with atheromatous plaque burden and future risk of clinical CHD events. These findings suggest that ET commenced in recently postmenopausal women may slow the development of atherosclerotic plaque.

Stroke

All studies indicate that postmenopausal HT is not effective for reducing the risk of a recurrent stroke among women with established cardiovascular disease (CVD) or for prevention of a first stroke, and may increase the rate of first strokes. HT cannot be recommended for the primary or secondary prevention of stroke.

Venous Thromboembolism

Growing evidence suggests that women with a prior history of VTE or women who possess factor V Leiden are at increased risk for VTE with HT use. There are limited observational data suggesting lower risks of VTE with transdermal than with oral ET, but there are no RCT data on this subject. Lower doses of oral ET may also confer less VTE risk than higher doses, but no RCT data are available to confirm this assumption.

Cardiovascular Effects Conclusion

Pending additional data, HT is currently not recommended as a sole or primary indication for coronary protection in women of any age. Initiation of HT by women aged 50 to 59 years or by those within 10 years of menopause to treat typical menopause symptoms (e.g., vasomotor, vaginal) does not seem to increase the risk of CHD events. There is emerging evidence that initiation of HT in early postmenopause may reduce CHD risk.

Diabetes Mellitus

Aging is associated with an increased risk of non-insulin-dependent diabetes mellitus (DM), also known as adult-onset DM or type 2 DM. Although no HT product has regulatory agency approval to treat DM, large RCTs suggest that HT use reduces the new onset of type 2 DM.

Optimal glucose control is a prime goal of therapy in postmenopausal women who have type 2 DM. Some data suggest that postmenopausal women with type 2 DM who use ET may require lower doses of medications for glycemic control.

In women with type 2 DM, measures to reduce CHD risk are probably of greatest concern. If HT is prescribed, the specific agent, dose, regimen, and route of administration are especially important. Transdermal ET administration may offer advantages over the oral route. Serum triglyceride levels, which are often increased in patients who have DM, are not increased further with transdermal

HT. Moreover, adverse alterations in blood pressure in both nonhypertensive and hypertensive women (although viewed as being a rare, if not idiosyncratic, reaction) have been reported only with oral therapy.

Endometrial Cancer

The use of unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the ET dose and duration of use. Standard-dose therapy (0.625 mg/d conjugated estrogen [CE] or the equivalent), when used for more than 3 years, is associated with up to a fivefold increased risk of endometrial cancer; if used for 10 years, the risk increases up to tenfold. This increased risk persists for several years after ET discontinuation. Because abnormal uterine bleeding usually brings the disease to medical attention early in its course, most cases do not reduce life expectancy. To negate this increased risk, adequate concomitant progestogen use is recommended for women with an intact uterus (see Progestogen indication, below, for more). There is limited evidence to support the use of HT in women with a history of early-stage (stages I and II) endometrial cancer.

Breast Cancer

Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years. Available evidence suggests that ET for fewer than 5 years has little impact on breast cancer risk. Specific subgroups may be affected in different ways.

EPT and, to a lesser extent, ET, increase breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms.

The question of HT use in women with a history of breast cancer is unresolved. The limited epidemiologic evidence is mixed; there are no completed long-term RCTs.

Mood and Depression

For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood. Several small, short-term trials among middle-aged women suggested that HT use improves mood, whereas other trial results showed no change.

Although HT might have a positive effect on mood and behavior, HT is not an antidepressant and should not be considered as such. Evidence is insufficient to support its use for the treatment of depression.

Cognitive Aging/Decline and Dementia

The term "cognition" describes the group of mental processes by which knowledge is acquired or used. It encompasses such mental skills as concentration, learning and memory, language, spatial abilities, judgment, and reasoning. Dementia is the progressive decline in cognitive function due to damage or disease in the brain

beyond what might be expected from normal aging. Alzheimer`s disease (AD) is the most common cause of dementia.

HT cannot be recommended at any age for the sole or primary indication of preventing cognitive aging or dementia. HT seems to increase the incidence of dementia when initiated in women age 65 and older. Similarly, HT should not be used to enhance cognitive function in younger postmenopausal women with intact ovaries, although very small clinical trials support the use of ET initiated immediately after menopause induced by bilateral oophorectomy. Available data do not adequately address whether HT used soon after menopause increases or decreases later dementia risk. Limited data do not support the use of HT as treatment of Alzheimer's disease.

Premature Menopause and Premature Ovarian Failure

Women experiencing premature menopause ($\leq$40 y) or premature ovarian failure are a distinctly different group than women who reach menopause at the typical age of 51.3 years. Premature menopause and premature ovarian failure are associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD. There are inadequate data regarding HT in these populations. Most reports suggesting an increased risk of CHD with early natural or surgical menopause also suggest a protective effect of HT. The existing data regarding HT in women experiencing menopause at the typical age should not be extrapolated to women experiencing premature menopause and initiating HT at that time. The risks attributable to HT use by these young women receiving HT are likely smaller and the benefits potentially greater than those in older women who commence HT at or beyond the typical age of menopause, although no trial data exist.

Total Mortality

The WHI trials are consistent with observational studies indicating that HT may reduce total mortality when initiated soon after menopause. The WHI suggests that both ET and EPT reduce total mortality by 30% when initiated in women younger than age 60, and when data from the ET and EPT WHI RCTs were combined, that reduction with HT use was statistically significant. In contrast, HT was not associated with mortality reduction among women who initiated HT at age 60 or older.

Practical Therapeutic Issues

Class Versus Specific Product Effect

Estrogens and progestogens share some common features and effects as well as potentially different properties. However, the current gold standard for determining the net clinical outcome for any given agent (alone or in combination) is through RCTs. In the absence of rigorous, head-to-head RCTs of various estrogens and progestogens, which are unlikely to be conducted, clinicians will be required to generalize the clinical trial results for one agent to all agents within the same hormonal family. On a theoretical basis, however, there are likely to be differences within each family based on factors such as relative potency of the compound, androgenicity, glucocorticoid effects, bioavailability, and route of administration.

Progestogen Indication

The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use. All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen. Postmenopausal women without a uterus should generally not be prescribed a progestogen with systemic ET. A progestogen is generally not indicated when ET at the recommended low doses is administered locally for vaginal atrophy. Concomitant progestogen may improve the efficacy of low-dose ET in treating vasomotor symptoms. Some women who use EPT may experience undesirable side effects from the progestogen component.

Dosages

The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman should be the therapeutic goal, with a corresponding low dose of progestogen added to counter the adverse effects of systemic ET on the uterus. Lower ET and EPT doses are better tolerated and may have a more favorable benefit-risk ratio than standard doses. However, lower doses have not been tested in long-term trials. Among the lower daily doses typically used when initiating systemic ET are 0.3 mg oral conjugated estrogen, 0.5 mg oral micronized 17 beta-estradiol, and 0.014 to 0.025 mg transdermal 17 beta -estradiol patch. The progestogen dose varies based on the progestogen used and the estrogen dose, typically starting at the lowest effective doses of 1.5 mg medroxyprogesterone acetate (MPA), 0.1 mg norethindrone acetate, 0.5 mg drospirenone, or 50 to 100 mg micronized progesterone. Different doses may have different health outcomes. Some women may require additional local ET for persistent vaginal symptoms.

Routes of Administration

There is currently no clear benefit of one route of administration versus another for systemic ET. Nonoral routes of administration may offer both advantages and disadvantages compared with the oral route, but the long-term benefit-risk ratio has not been demonstrated. Differences would be related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of ingredients. There is observational evidence that transdermal ET may be associated with a lower risk of deep vein thrombosis (DVT) than oral administration but no RCT evidence. Local ET administration is preferred when treating solely vaginal symptoms. Although minimal systemic absorption is possible, there are no reports of adverse effects.

Systemic progestogen is required for endometrial protection from unopposed ET. Topical progesterone is not recommended. (For more, see Progestogen indication, above.)

Regimens

There are multiple dosing regimen options for endometrial safety when adding progestogen to estrogen (see Table 3 in the original guideline document). Research is inadequate to endorse one regimen over another. Current data support the recommendation to minimize progestogen exposure through one of

various options. There is insufficient evidence regarding endometrial safety to recommend as an alternative to standard EPT regimens the off-label use of long-cycle regimens, vaginal administration of progesterone, the contraceptive levonorgestrel-releasing intrauterine system, or low-dose estrogen without progestogen. If any of these approaches is used, close surveillance of the endometrium is recommended pending more definitive research, much of which is currently in progress.

There are also multiple dosing regimen options from which to choose when using ET alone for women after hysterectomy; no data provide guidance on which regimen is best for all women.

"Bioidentical" Hormones

NAMS recognizes that one area of confusion in clinical practice is so-called "bioidentical" hormone preparations. This term has been used to refer to many well-tested, regulatory agency-approved, brand-name HT products containing hormones chemically identical to hormones produced by women (primarily in the ovaries), such as 17 beta-estradiol or progesterone. However, the term is most often used to describe custom-made HT formulations (called "bioidentical hormone therapy," or BHT) that are compounded for an individual according to a healthcare provider`s prescription.

NAMS recommends that filled prescriptions for bioidentical hormone therapy (BHT) should have a patient package insert identical to that required for products that have regulatory agency approval. In the absence of efficacy and safety data for any specific prescription, the generalized benefit-risk ratio data of commercially available HT products should apply equally to BHT. There are individual women for whom the positives outweigh the negatives, but for the vast majority of women, regulatory agency—approved HT will provide appropriate therapy without assuming the risks and cost of custom preparations.

Treatment Issues

Pretreatment Evaluation

HT should be considered only when an indication for therapy has been clearly identified, contraindications ruled out, and the potential individual benefits and risks adequately discussed with the woman so that an informed decision can be made. Before initiating HT, a comprehensive history and physical examination are essential. Mammography should be performed according to national guidelines and age, but preferably within the 12 months before initiation of therapy. Other specific examinations, such as bone densitometry, may be considered on a case-by-case basis.

Timing of Initiation

Women older than age 60 who experienced natural menopause at the typical age and have never used HT will have elevated baseline risks of CHD, stroke, VTE, and breast cancer, and HT should therefore not be initiated in this population without a compelling indication and only after appropriate counseling.

Premature menopause and premature ovarian failure are conditions associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD, but there are no clear data as to whether ET or EPT will affect morbidity or mortality from these conditions. Despite this, it is logical and considered safe to recommend HT for these younger women, at least until the typical age of natural menopause. Younger women with premature menopause might also require higher doses of HT for menopause symptom relief than the doses currently recommended for women aged 50 to 59 years.

Duration of Use

Provided that the lowest effective dose is used, that the woman is well aware of the potential benefits and risks, and that there is clinical supervision, extending HT use for an individual woman's treatment goals is acceptable under some circumstances, including:

- The woman for whom, in her own opinion, the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop HT
- Regardless of symptoms, for further prevention of osteoporotic fracture and/or preservation of bone mass in the woman with established reduction in bone mass when alternate therapies are not appropriate, cause unacceptable side effects, or when the benefit-risk ratio of the extended use of alternate therapies is unknown.

Symptom Recurrence

Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use. The decision to continue HT should be individualized on the basis of severity of symptoms and current benefit-risk ratio considerations, provided the woman in consultation with her healthcare provider believes that continuation of therapy is warranted.

Discontinuance

Current data suggest that the rates of vasomotor symptom recurrence are similar when HT is either tapered or abruptly discontinued.

There is an obvious disparity in two reports on breast cancer incidence after discontinuation of HT; in the absence of any current conclusion, neither report should influence clinical decisions regarding current HT usage beyond those reported in this North American Menopause Society position statement.

Individualization of Therapy is Key

An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks, but it cannot be assumed that benefits and risks of HT apply to all age ranges and durations of therapy. Women`s willingness to accept risks of HT will vary depending on their individual situations, particularly whether HT is being considered to treat existing symptoms or to lower risk for osteoporotic fractures that may or may not occur. Moreover, because incidence of disease outcomes increases with age and time

since menopause, the benefit-risk ratio for HT is more likely to be acceptable for short-term use for symptom reduction in a younger population. In contrast, long-term HT or HT initiation in older women may have a less acceptable ratio. Women experiencing premature menopause, whether natural or induced, have a different situation, including increased risk of osteoporosis and cardiovascular disease, and often more intense symptoms, than women reaching menopause at the typical age. Recommendations would be different for women who are first users of HT or women who are in their sixties and have previously used HT for several years. Each woman is unique, having her own risk profile and preferences. When HT is desired by patients, individualization of therapy is key to bringing health benefits with minimal risks, thereby enhancing QOL.

Summary

The potential absolute risks published thus far for use of HT are low, particularly for the WHI ET trial, which provided evidence of considerable safety for 0.625 mg/day of oral conjugated estrogen. The risks in the WHI EPT trial were rare by the criteria of the Council for International Organizations of Medical Sciences (CIOMS), except for stroke, which was above the rare category. For women younger than age 50 or those at low risk of CHD, stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk or benefit from ET or EPT is likely to be even smaller than that demonstrated in the WHI, although the relative risk at different ages may be similar. There is a growing body of evidence that each type of estrogen and progestogen, route of administration, and timing of therapy have distinct beneficial and adverse effects. Further research remains essential.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of estrogen therapy/estrogen-progestogen therapy (ET/EPT) for treatment of menopause-related symptoms and prevention of disease

POTENTIAL HARMS

- In the short term, hormone therapy (HT) may possibly be associated with an increase in coronary heart disease (CHD) risk among women who are more distant from menopause at the time of HT initiation.
- Results of observational studies of the risk of stroke with HT have been inconsistent. Several indicated an increased risk of ischemic stroke, whereas

others showed no effect on stroke risk. The Women's Health Initiative estrogen-progestogen therapy (EPT) and estrogen therapy (ET) trials demonstrated an increased risk of ischemic stroke and no effect on hemorrhagic stroke.

- Data from both observational studies and randomized controlled trials (RCTs) suggest an increased risk of venous thromboembolism (VTE) with oral HT.
- The use of unopposed systemic ET in postmenopausal women with an intact uterus is associated with an increased endometrial cancer risk related to the ET dose and duration of use.
- Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years. EPT and, to a lesser extent, ET, increase breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms.
- Progestogens in EPT may worsen mood in some women, possibly in those with a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression.
- The risks in the WHI EPT trial were rare by the criteria of the Council for International Organizations of Medical Sciences (CIOMS), except for stroke, which was above the rare category. For women younger than age 50 or those at low risk of coronary heart disease (CHD), stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk from estrogen therapy (ET) or EPT is likely to be even smaller than that demonstrated in the WHI, although the relative risk at different ages may be similar.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This position statement focuses on the use of hormone therapy (HT) products available by prescription in the United States and Canada. A current listing of these products is posted on The North American Menopause Society (NAMS) Web site (http://www.menopause.org/edumaterials/hormoneprimer.aspx) This paper does not include other hormones, such as estrogen agonists/antagonists (formerly called selective estrogen-receptor modulators), those available without a prescription (including phytoestrogens), and testosterone therapy, the latter having been addressed in a previous NAMS position statement.
- The Society's position statements provide expert analysis of the totality of the data, including the most recent scientific evidence, in an attempt to assist healthcare providers in their practices. They do not represent codified practice standards as defined by regulating bodies and insurance agencies.
- Limitations (of the literature search) included a scarcity of randomized prospective study data on the consequences of long-term use of HT when prescribed for symptom management or disease risk-reduction outcomes. In addition, evidence-based medicine implies that recommendations be limited to the women for whom the studies are relevant. Although this goal is ideal in principle, it is impossible in practice, given that there will never be adequate randomized, controlled trials (RCTs) to cover all populations, eventualities, drugs, and drug regimens. The practice of medicine is ultimately based on the interpretation at any one time of the entire body of evidence currently available.

- NAMS recognizes that no trial data can be used to extrapolate clinical management recommendations for all women and that no single trial should be used to make public health recommendations. There are many observational studies, but, because the trials within the Women's Health Initiative (WHI) are for some outcomes the only large, relatively long-term randomized controlled trials to date of postmenopausal women using HT, there was a necessity to give these findings prominent consideration among all the studies reviewed in the development of this paper. It is also recognized that the WHI trials have several characteristics that limit the ability to generalize the findings. These include the use of only one formulation of estrogen (conjugated estrogens [CE]), alone or with one progestin (medroxyprogesterone acetate [MPA]), and only one route of administration (oral). Moreover, women studied in the WHI were older (mean age, 63 years)—mostly more than 10 years beyond menopause, with more risk factors than younger women who typically use HT for menopause symptoms. They were also largely without menopause-related symptoms.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Utian WH, Archer DF, Bachmann GA, Gallagher C, Grodstein F, Heiman JR, Henderson VW, Hodis HN, Karas RH, Lobo RA, Manson JE, Reid RL, Schmidt PJ,

Stuenkel CA. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. Menopause 2008 Jul-Aug;15(4 Pt 1):584-602. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Oct 6 (revised 2008 Jul)

GUIDELINE DEVELOPER(S)

The North American Menopause Society - Private Nonprofit Organization

SOURCE(S) OF FUNDING

The North American Menopause Society (NAMS)

GUIDELINE COMMITTEE

Advisory Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Advisory Panel Members

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Cynthia A. Stuenkel, MD, Clinical Professor of Medicine, University of California, San Diego, La Jolla, CA

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

For the Advisory Panel:

Dr. Archer reports: Consultant—Agile, Berlex, Johnson & Johnson, Novo Nordisk, Organon, Ortho-McNeil, Pfizer, Solvay TAP, Wyeth; Research support—Barr/Duramed, Berlex, Organon, Solvay, Warner Chilcott, Wyeth; Speaker—Novo Nordisk, Organon, Wyeth.

Dr. Bachmann reports: Research support—Bayer, Boehringer-Ingelheim, Boston Scientific, Duramed, GlaxoSmithKline, Johnson & Johnson, Novartis, Novo Nordisk, Pfizer, Procter & Gamble, Roche, Wyeth, Xanodyne.

Dr. Gallagher reports: Research support—Pfizer, Wyeth; Speaker—Wyeth.

Dr. Grodstein reports: No significant financial relationships.

Dr. Heiman reports: Consultant—Bayer, Boehringer-Ingelheim; Research support—Bayer, Pfizer.

Dr. Henderson reports: No significant financial relationships.

Dr. Hodis reports: No significant financial relationships.

Dr. Karas reports: Consultant, Speaker—Wyeth.

Dr. Lobo reports: Consultant—Bayer, Organon, Ortho, Solvay, Wyeth.

Dr. Manson reports: No significant financial relationships.

Dr. Reid reports: Advisory board—Wyeth Canada; Consultant—Bayer Canada, Procter & Gamble; Speaker—Bayer Canada, Wyeth Canada.

Dr. Schmidt reports: Research support—Novogen, Watson.

Dr. Stuenkel reports: Consultant—Upsher-Smith, Wyeth; Speaker—Upsher-Smith, Eli Lilly.

Dr. Utian reports: Advisory board/consultant—GlaxoSmithKline, Merck, Orcas; Consultant—Barr/Duramed, Berlex, Bionovo, Bradley, Depomed, KV Pharmaceuticals, Novo Nordisk, Organon, Pfizer, Gerson Lehman, Goldman Sachs, Johnson & Johnson, McKinsey, Wyeth

For members of the North American Menopause Society (NAMS) Board of Trustees who are not serving on the Advisory Panel:

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Ms. Contestabile reports: No significant financial relationships.

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Dr. Goldstein reports: Advisory board—Eli Lilly, GlaxoSmithKline, Merck, Pfizer, Procter & Gamble.

Dr. Kagan reports: Advisory board—Merck; Consultant—Merck, Roche/GlaxoSmithKline; Research support—Amgen, Aventis, Eli Lilly, Novartis, Procter & Gamble, Roche/GlaxoSmithKline, Wyeth; Speaker—Merck, Roche/GlaxoSmithKline.

Dr. Pinkerton reports: Consultant—Boehringer-Ingelheim, Duramed, Merck, Novo Nordisk; Research support—Solvay, Wyeth; Speaker-Merck.

Dr. Reame reports: Consultant—Cypress Bioscience, Procter & Gamble; Research support—Novo Nordisk, Procter & Gamble.

Dr. Rothert reports: No significant financial relationships.

Dr. Schiff reports: Advisory Board—*Pause*, the consumer magazine of the American College of Obstetricians and Gynecologists; Editor-in-chief—*Menopause*, the official journal of The North American Menopause Society.

Dr. Speroff reports: Consultant—Warner Chilcott; Research support—Barr, Berlex, Organon, Wyeth.

Dr.Warren reports: Research support—GlaxoSmithKline, Novartis, Solvay, Wyeth; Speaker—Bayer, Bradley, Wyeth.

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Ms. Boggs reports: No significant financial relationships.

Dr. Loprinzi reports: No significant financial relationships.

Ms. Wisch reports: No significant financial relationships.

Ms. Wysocki reports: Advisory Board-Berlex, Digene, Duramed, Esprit, Eli Lilly, Merck, Organon, Ortho Women`s Health, Wyeth.

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American Medical Women's Association
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National Association of Nurse Practitioners in Women's Health - Professional Association
National Women's Health Resource Center - Private Nonprofit Organization
Society of Obstetricians and Gynaecologists of Canada - Medical Specialty Society
The Endocrine Society - Disease Specific Society

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: The North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause* 2007 Jan 31;14(2):168-82. [145 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from The North American Menopause Society (NAMS) Web site.

Print copies: Available from NAMS, P.O. Box 94527, Cleveland, OH 44101, USA. Order forms are available in Portable Document Format (PDF) from The North American Menopause Society (NAMS) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Key points: NAMS July 2008 position statement on hormone therapy. Slide set. 2008 Jul. 46 p. Available from The North American Menopause Society (NAMS) Web site.
- Boggs PP, Utian WH. The North American Menopause Society develops consensus opinions. Menopause 1998 Summer;5(2):67-8. Available from the NAMS Web site.

PATIENT RESOURCES

None available

NGC STATUS

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